Thesis for Doctor of Philosophy Degree in the Faculty of medicine

Bundelkhand, University,
Jhansi (India)

A Study of childhood Epilepsy and Epileptic Syndromes in a subset of population in India with emphasis on hereditary factors.

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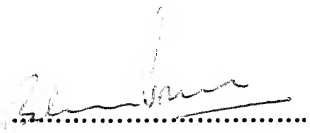

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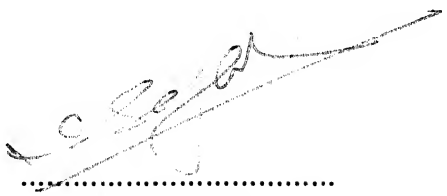

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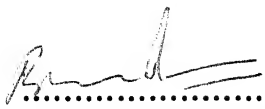
On.....



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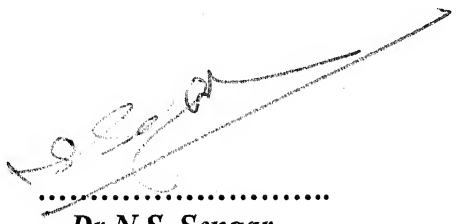

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Declaration

I declare this study is substantially my own original work and has not been submitted in any form for an award at any other academic institution.

Signature.....

Dr Brahm Prakash

Acknowledgement

I would like to avail this opportunity to place on record my heart felt thanks to all those who helped me in completion of this study.

I express my sincere gratitude to the authorities of Bundelkhand University and Prof. Ramesh Chandra in particular in allowing me to pursue this study in children.

I am extremely grateful to Dr N.S. Sengar for guiding and supervising the work without whose suggestions and overall supervision it was not possible to complete this study.

I am grateful to Dr K.K. Gupta Medical director NRCH for continuous support and encouragement for the study of epilepsy in children at central hospital New Delhi.

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I do not have words and means to repay the debt of Prof. Satish Jain in introducing me to the research methodology in epilepsy during my earlier work "Classification of Seizures in children".

I will be failing in my duty if I do not mention the encouragement and support which I got from Dr K.Suresh D.G./RHS for my study. It was his persistent motivation, which encouraged me to take up this work.

I do not have words to express my thanks to my sons Vaibhav and Anubhav. They have never complained in my devoting the time for this study, which I should have given to them. I am also thankful to them for resquing me whenever I had problem on computer while compiling this work.

Last but not the least it was not possible to complete this study without constant love, care and strength which my wife Vinod gave me. In fact she was the force behind motivating me constantly to compete this work.

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Dr Brahm Prakash

List of Contents

Introduction & Review of Literature

A study of childhood Epilepsy and Epileptic Syndromes in a subset of population in India with emphasis on hereditary factors.

Seizure is a common neurological disorder in pediatric age group and occurs in 3-5 % of children. Epilepsy is a chronic condition characterized by more than one recurrent, unprovoked sudden seizure and constitutes a large percentage of pediatric neurological problems. Epilepsy occurs in 0.5-1.0 % of the population and begins in childhood in 60% of cases (Nelson textbook of pediatrics 16th edition 2000). The classification of epileptic seizures has contributed to the rational use of anti-epileptic drugs for various types of seizures (Fritz E. Derives-clinical aspects of epilepsy Cleveland clinic journal of medicine). The classification of epileptic seizures and epileptic syndromes also helps in predicting the prognosis of a given type of epileptic syndrome and also give an idea regarding duration of administration of antiepileptic drug. A major contribution of International League against Epilepsy was the recommendation of standardized classification and terminology for epileptic seizures and syndromes. This provided a universal vocabulary that not only facilitated communication among clinicians, but also established a taxonomic foundation for basic research on epilepsy (ILAE Epilepsy Classification and Terminology-http //www.epilepsy.org/ctf/over-frame.html).

The International classification of seizures was first adopted in 1970 by the ILAE. It was further revised in 1981 and designed mainly to minimize any descriptive ambiguities and took into consideration only the clinical form, ictal and interictal EEG.

Classification of seizures1981:

1. *Partial Seizures*

- *Simple (consciousness not impaired) – With motor, somatosensory, special sensory, autonomic or psychic symptoms.*
- *Complex (with impairment of consciousness-Beginning as simple partial seizures, progressing to complex seizures with or without automatism. May progress to become secondarily generalized.*

II. Generalized seizures

- *Absence seizures (typical or atypical)*
- *Myoclonic seizures*
- *Clonic, tonic or tonic- clonic seizures*
- *Atonic seizures.*

III Unclassified seizures.

- *Whether partial or generalised*

The limitation of this classification was it was confined to an individual seizure type. Seizure is an event with which a patient comes to a physician but the condition to which this seizure belongs is the epileptic syndrome and it is also the language in which two physicians can communicate. The International Classification of epileptic seizures and epileptic syndromes 1985/1989(Commission on Classification and Terminology of the International League against epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989,30; 389-399) tried to overcome the shortcomings of the previous classifications.

This Classification was exciting because in recognizing electroclinical syndromes early in the diagnosis of epilepsy, it was possible to predict response to treatment and more so the prognosis.

The syndromes:

Syndromes are clusters of signs and symptoms customarily occurring together and include:

- *The clinical picture of seizure*
- *The age of patient at the time first seizure*
- *EEG*
- *Evolution and prognosis*
- *Associated neurological features*
- *Positive or negative family history*
- *Neuroimmaging investigative studies.*

Two dichotomies are used in this classification-

Localization related onset or generalised

Etiology known or unknown:

Idiopathic: no underlying causes, may be inherited

- *Symptomatic:*

As a consequence of known or a suspected disorder of CNS

- *Cryptogenic:*

Cause is hidden or occults whereas in there do not fulfil the criteria for idiopathic while on the other hand there is no proof of their symptomatology.

*The symptomatic epilepsies constitute about 48% while 52% are idiopathic in nature. The incidence of symptomatic is higher then reported in the developed countries (Oka E, Ishida S, Ohtsuka Y, Othara S. Classification of epilepsies and epileptic syndromes of childhood according to the 1989 ILAE classification. J epilepsy 1993; 6:272-6). This is mainly because of higher incidence of perinatal insult and CNS infections. The insults to the nervous system in the neonatal period account for nearly one third of all symptomatic cases (Eriksson KJ, Koivikko MJ. Prevalence, Classification, and severity of epilepsy and epileptic syndromes in children. Epilepsia 1997; **38** : 1275-82)*

The other cause of symptomatic epilepsy are tumors, intracranial granulomas, trauma, vascular srokes, AV malformation, congenital malformation, inborn error of metabolism etc (Viani F, Beghi E, Atza G, Gulotta MP.Classification of epileptic syndromes: advantage and limitations for evaluation of childhood epileptic syndromes in clinical practice. Epilepsia 1988; 29:440-5.)

Over the last decade, epidemiological studies have demonstrated that the prognosis of many childhood epilepsies is more favorable with 70-80 % reaching remission. However sever cases, some of which are refractory to treatment account for 20-30% of all cases (Eriksson KJ, K Koivikko MJ. Prevalance, classification and severity of epilepsy and epileptic syndromes in children. Epilepsia1997; 38:1275-82).

Incidence:

Incidence is the rate at which new cases of a condition occur in a population. The incidence of epilepsy for all age group is about 40/100,000 persons years (Hauser WA, Angers JF, kurlandLT. The incidence of epilepsy in Rochester, Minnesota 1935-79. Epilepsia 1984:25:666).

The age specific incidence of unprovoked seizers in virtually all studies is highest in the first month of life. Seizure incidence then remains relatively high but it declines during the first year of life, and tends to decrease slightly thereafter through the second decade, after which incidence remains constant at about 30/100,000 in the adult years, only to increase again after the age of 60.

Contrary to common opinion, only about 50% of all cases of epilepsy start in childhood. In most studies, about 60% to 70% of cases are of unknown cause and in childhood, the majority of new cases in children involve generalized seizures from onset. Most, total population studies of incidence report a slight male preponderance.

In a study by W. Allen Hauser from National Institute of Neurological Disorders and Stroke, Bethesda, the large pediatric population was followed from the first prenatal visit of the mothers in pregnancy until children born of those pregnancies were 7 years old. The study was sampled by the Collaborative Perinatal Project (NCPP) of the National Institute of Neurological and Communicative Disorders and Stroke, provided valuable information regarding the epidemiology of epilepsy. In that population, 8.0 white children per thousand had at least one nonfebrile seizure, not considered being symptomatic of acute neurologic illness, between the ages of 1 month and 7 years. This is similar to the cumulative incidence for one or more unprovoked seizures of 1.1% by age 10 in the population of Rochester Minnesota. In black children in the NCPP study, the cumulative incidence rate was 9.0 per thousand. The difference between the racial groups was not statistically significant. Seizures occurred with similar frequency in boys and girls of the two racial groups. Minor motor seizures and neonatal seizures were not different in frequency by race or sex. (Clinical aspect of pediatric epilepsy volume 56 suppl., part 2)

Age –specific incidence rate (Rochester, Minnesota, 1935-1979)

Age group	***No patients***	***rate/100,000***	***proportion***	***Male/Female***
Years		***Persons-years***	***Idiopathic%--Partial%***	***%***
<1	*41*	*121*	*54*	*17*	*120*
1-4	*85*	*63*	*81*	*21*	*97*
5-14	*129*	*44*	*84*	*47*	*123*

Prevalence:

Prevalence of epilepsy is a measure of the proportion of patients currently suffering from active epilepsy or experiencing the consequences of epilepsy as measured by taking anticonvulsant. Since one need to identify existing cases of the illness, prevalence studies are considerably easier to conduct than incidence itself. The estimated prevalence of epilepsy varies widely in reported studies by a factor of 20, and ranges from a low of 2/ 100 0 in Marianas islands (Stanhope JM, Brody JA, Brink E. Convulsions among the Chamorro peoplle of Guam, Marianas Islands. I. Seizure disorders Am J Epidemiology 1972; ***95****: 292-298) to a high of 37/10,000 in Nigeria (*Osunto kun Bo, Aevja AOJ, Nottidge VA, et al. Prevalence of the epilepsies in Nigerian Africans: a community-based study, *Epilepsia 1987;* ***28****:272-279). Unfortunately this variation seems more related to study methodology and to definitions of epilepsy in individual studies than to true population variations. In prevalence studies based upon incidence cohorts, prevalence tends to increase with advancing age through early childhood, only to stabilize in the teen age and young adult years (Hauser and Nelson, Epidemiology of epilepsy; Cleveland clinic journal of Medicine: Volume 56 Suppl. Part 2).*

Febrile convulsions:

Febrile convulsions are the commonest type of genetic abnormality. 5% of all children will have a fit under five years of age, 3% of whom fulfil the criteria for febrile covulsions. The incidence is higher in Japan at 7-8% (Forfar and Arneil's Textbook of Pardiatrics1998 fifth edition, Churchill Livingstone, London).

Febrile convulsions rarely develop in to epilepsy, and they spontaneously remit without specific therapy. They have uniformly excellent prognosis. Febrile seizures are age dependent and are rare before 9 months and after 5 years of age. The peak age of onset is 14-18 months of age, and incidence approaches 3-4% of young children. A strong family history of febrile convulsion in sibling and parents suggests a genetic

predisposition. Linkage studies in several large families have mapped the febrile seizure gene to chromosome 19p and 8p 13-21. An autosomal dominant inheritance pattern is demonstrated in some families (Nelson Textbook of Pediatrics16th edition, Harcourt Asia pte Ltd. 2000, Singapore.)

Risk of recurrence: 33% of all children with febrile convulsion will have recurrence of these 9% will have >3 recurrences, 75% of recurrences would occur within 1 year of first episode and 90% within 2 years (Nelson KB, Ellensburg JH. Prognosis in children with febrile seizures. Pediatrics 1978; 61:702-7.) The best predictor is early age of seizure and positive family history of febrile seizure(Berg AT, Shinar S, Hauser WA, ET AL. Predictors of recurrent febrile seizure: a meta –analytic review. Pediatric 1990; 116: 329-37).

Risk of subsequent epilepsy:

The overall risk of epilepsy after febrile seizure is 2-2.5% (Verity CM, Golding J. Risk of epilepsy after febrile convulsion: A national cohort study. Br Ed J 1991; 303: 1373 –6.) The prognosis is more guarded if the convulsion is prolonged or atypical .Up to 40% may have another convulsion and 15% a third episode. If the child suffers from multiple repeated febrile convulsions the possibility of early malignant epilepsy such as myoclonic epilepsy of Dravet exists.

The risk factors for subsequent epilepsy are

- *The child is less than 12 months old;*
- *Complex febrile seizure occurred with neurological sign*
- *Prolonged seizure lasts more than 30 minutes.*
- *Developmental/ neurological abnormality present before first seizure.*
- *There are more than three episodes*
- *Non febrile seizure in parents/ siblings.*

The risk of developing epilepsy in late years is more if two or more risk factors are present.

If two or more risk factors are involved, the possibility of risk of epilepsy is more approximately 9 to 10 percent. The subsequent epilepsy may be due to mesial temporal sclerosis due to recurrent seizures. EEG after febrile seizure will be abnormal in one third of cases after one week. Posterior slow wave activity may be bilateral or unilateral. Such abnormalities are not helpful in predicting subsequent epilepsy. The EEG after five years of age often shows abnormality such as spikes and wave activity which indicates a genetic predisposition but not that the child has epilepsy.

The etiologies which underlie the development of epilepsy in childhood vary in an age dependent fashion. Seizures in neonates, infants, and toddlers most frequently result from perinatal brain injury, congenital central nervous system malformations, and metabolic derangements. Central nervous system infection, genetic epilepsies, and neurodegenerative disorders are more likely to present with seizures beginning in later childhood. These causes stand in stark contrast to the adult population, where traumatic brain injury, cerebrovascular disease, and neoplasm represent the most frequent causes of seizures.

Hereditary factors in epilepsy and febrile seizures:

Genetic influence clearly plays role in febrile seizures. Children with positive family history of febrile seizure are more likely both to experience a febrile seizure (Berg et al., 1995; Bethune et al., 1993) and to experience recurrent febrile seizures (Annegers et al., 1990;Berg et al, 1997:1992:1990: Nelson and Ellenberg. 1978: Offringa et al1994: 1992) than children without such a family history. In a study of 32 twin pairs and 673 sibling relationship cases. Tsuoi 1987 reported a concordance rate of 56% in monozygotic and 14% in dizygotic twins. Clinical symptoms including age of onset and degree of fever were larger in the twin pairs than in the sibling relationship patients. The results were consistent with a multifactorial mode of inheritance for febrile convulsions. This was the case in an analysis of the Rochester, Minnesota, data set (Rich et al., 1987)

There may well be a subset of children who have an autosomal –dominant mode of inheritance of febrile seizures (Joshin et al.,) and Rich et al., 1987. At this time no definitive identification of a gene or locus for febrile seizure has been established. Genes on chromosomes 8 (Wallace et. al., 1996) and 19(Johnson) have been linked to some cases of febrile seizures in large families. Rapid advances in this area in future are anticipated. Most likely all children have some increased susceptibility to seizures from fever at the specific age window. Genetic influences are therefore likely to account for some but not all of the cases.

There is little doubt that epileptic seizures tend to aggregate in families (Hauser WA et all- clinical Aspects of Pediatric Epilepsy –Clevland Clinic Journal of Medicine Vol. 56 Suppl. Part 2pp115-193). While a number of diseases follow Mendelian pattern of inheritance and have as part of their manifestation the occurrence of seizures, these conditions, in aggregate, will account for no more than 1% of seizures in childhood (Anderson VE, Hauser WA, Rich SS, Genetic heterogeneity in the epilepsies (In) Degado-Escueta AV, Ward AA JR, Woodburry DM, Porter RJ, eds The mechanism of epilepsy. New York, Raven Press, 1986,pp59-75.). Risk for epilepsy is increased by a factor of three for individuals with a first degree relative with epilepsy, an overall risk similar to that associated with head injury or infection of the central nervous system (CNS)(Annegers J F, Hauser WA, Anderson VE, kurland LT, The risk of seizure disorders among relatives of patients and childhood on sent epilepsy Neurology 1982; 32; 174-179). Similarly, risk for epilepsy is increased by a factor of three for children with a sibling who has had febrile seizure (Annergers JF, Hauser WA, Anderson VE, Kurland LT. The risk of seizure disorders among relatives of patients with childhood onset epilepsy, Neurology 1982; 32:174-179). While there is a perception that generalized – onset seizures are associated with higher risk for epilepsy in relatives, this seems a result of very high risk among siblings with epilepsy manifested by absence seizures or Myoclonic seizures. If these unique but rare subgroups are excluded, risk for epilepsy among relatives of probands with epilepsy characterized by generalized – onset seizures are similar to those in relatives of probands with epilepsy manifested by partial seizures. Family history is important in modifying risk for epilepsy even in the presence of a history of overt cerebral insult.

In the study by Collaborative Perinatal Project (NCPP) of the National Institute of Neurological and communicative Disorders and stroke, familial factors were also predictors of seizure disorder in children. Family history factors showing significant uinivariate association with seizure disorders included maternal seizure disorders, maternal MR, Paternal congenital malformations, and seizures or motor deficits in older siblings. Paternal seizures were not observed to be predictive; however, histories were taken from mothers who might not always have been acquainted with the fathers medical histories except in one mother child pair with tuberous sclerosis, specific heritable disorders were not recognized (Nelson KB, Ellen Berg JH. Predisposing and causative factors in childhood epilepsy. Epilepsia1987; 28(suppl); S16-S24).

The familial tendency is thought to be carried on chromosome 6 and to be age dependent in its manifestation. Unless EEG studies with hyperventilation and photic provocation are carried out between 3 and 15 years one may miss the dominant transmission, as clinical seizure may not occur. Precipitation of seizure by computer game has reinforced this as an important area. Lennox 50 years ago showed that the number of the close relatives with an epileptic EEG was six times higher with known epileptics than with normal controls (Forfar and arneil's Text book of Pediatrics, Churchill Living stone5th editionpp677-680).

Genetic diseases with seizures a symptom there are more than 200 Mendelian conditions with epilepsy as main symptom. Tuberous sclerosis is a good example of how a genetic disease may present as any one of the three clinical form i.e. genetic, lesional or malignant.

- *There is incomplete penetrance so uncomplicated epilepsy may occur in members of the family without any other clinical manifestation of the diseases.*
- *Single or multiple small galiomas, hamartomas and tubers act as focal 'lesions'.*
- *Malignant epilepsy such as west's syndromes or Lennox-Gastaut syndromes can occur in the infant of a tuberous sclerosis mother, especially after several*

generations. Dominant inheritance causes worse disease when acquired from the mother and may result in brain malformation with cortical dysphasia.

Some EEG studies suggest that the generalized spikes and wave EEG pattern in the inherited as an autosomal dominant trait with age-dependent expression. Other workers have suggested that polygenic inheritance is a better explanation of the data. The risk for sibling of patient with generalized epilepsy ranges from 4% to 8% which is substantially lower than would be expected from a simple gene disorder. Partial epilepsies have often been regarded as nongenetic or lesional types of epilepsy. However, certain types do show clear genetic influence. These include benign partial epilepsies of childhood and posttraumatic epilepsy.

Sibling and offspring of the affected probands have three to four fold increase in the febrile convulsion rate compared with the general population. Interpretation of the family studies on febrile convulsions has resulted in the conflicting conclusions. The inheritance said to be autosomal dominant, autosomal recessive or polygenic. The relationship of the febrile convulsion to epilepsy is complex and there is some evidence that there may be two genetically distinct subtypes of febrile convulsions with different risk of the subsequent epilepsy. In addition many children with febrile convulsion will subsequently show generalized spikes and wave on EEG even though they do not have convulsion, as do a high proportion of siblings.

By discovering a linkage between juvenile myoclonic epilepsy and HLA markers, the gene responsible was successfully mapped to human chromosome 6p (Durner et al 1991). The locus was subsequently designated EJM1.than by virtue of the close association of juvenile myclonic epilepsy and other generalized epilepsy disorder (childhood pyknolaptic absence epilepsy (typical absence epilepsy), grand mall Seizures on early morning awakening, photo convulsive television or video games epilepsy), together with the high incidence of EEG abnormality in the close relatives, investigators concluded that the gene imparts a tendency for abnormal electrical activity to synchronize and generalize in histologically normal cerebral cortices.

The various epileptic syndromes are actually the different ways in which this tendency expresses itself (Delgado- Escueta et all 1990, Greenberg et al

1995). Juvenile myoclonic epilepsy can be considered the prototype, which has a mixture of all three types of absence, myoclonic and generalized tonic-clonic fits, while the rest are milder variants. The expression of the gene is highly age dependent, just, as childhood absence epilepsy tends to resolve after adolecene. EEG can not reliably do family screening. As it may be absent in older individuals linkage or DNA analysis may be necessary.

A recent report of a linkage study showed no evidence for a locus on chromosome 6p in some British and Swedish families with juvenile myoclonic epilepsy and primary Gradmall seizures (Whithouse et al 1993). It is therefore reasonable to conclude that there is more then one gene carrying the tendency for generalized fits. It is interesting to note that valproic acid is an effective anti epileptic drug for these syndromes. It is differrent from drugs in that it is a fatty acid with eight carbon molecules. Eight carbon fatty acids are anticonvulsant and ten carbon fatty acids are anaesthetic agents. Octanoic acid was thought to be the fatty acid with anti epileptic properties in the ketigenic diet.

The fact that valproic acid appears specific for many genetic epilepcies suggest that it may correct an underlying metabolic abnormality. Hope fully gene cloning will provide insight in to the mechanism of the fits as well as the anti epileptic action of valproic acid. (Forfar and Arneil's Text book of Pediatrics, fifth edition, Churchil living stone, pp681 to 682

Hypoglycemia, hypocalcaemia or hypomagnesemia will not be included in this group. These are acute dysrhythmias, which complicate acute encephlopathy, which may be recurrent, and not simply the seizure. Conditions such as mitrochondrial encephlopathy with lactic acidosis and stork like episodes (MELAS syndrome). And Myoclonic epilepsy with ragged red fibers (MERRF) is included. These disorders have either a known enzyme defect or morphological evidence of storage abnormality but the enzyme defect is still unknown. They are almost invariably associated with other neurological abnormality, particularly intellectual deterioration. Thus the presence of family history with a symptomatic combination of seizure and mental retardation should trigger a search for inborn errors of metabolism as this has implications for treatment and genetic counseling.

Following is the list of genetic epilepsies:

- ***-Benign familial neonatal seizure – AD:***

  Chromosome 20, nonsence mutation of acetylene receptor (leppert et al 1989)

  Normal development

- ***-Idiopathic partial epilepsy of infancy-50% family history:***

  related to dominant neonatal fit

  Neurology normal

  Others on chromosome 19

- ***-Benign myoclonic epilepsy of infancy***

  -AR seen in identical twins,

  valproate sensitive,

  normal development.

- ***-Childhood Absence epilepsies -AD:***

  variable penetrance and age

  nearly normal Dependent

  expression; 60-70% female

- ***-Photosensitive epilepsy:***

  - Genetically inherited and

  -Amenable to valproate

  -Normal neurology

  -More common in females

  Photosensitivity persists inspite of treatment

- ***-Epilepsy with myoclonic absence***

  -Male preponderance

  -Neurology exam normal,

  - mental Retardation in 45 to 75% cases

- ***Juvenile absence epilepsy***

  -Good response to Valproate

-Normal neurology

- ***Juvenile myoclonic epilepsy***

  -Chromosome 6,

  Excellent response to Valproate,

  Normal Neurology

- ***Benign rolandic epilepsy :***

  with variable penetrance age dependent

  Absence of neurological and intellectual deficit

- ***Benign occipital with occipital spike-waves***

  -Difficult to treat

Source: *Disorders of central nervous System, Forfar and Arneil's Textbook of Pediatrics Churchill Living stone fifth edition 1998,pp680-681.*

A study by S.Jain, MV Padma, A Puri, Jyoti and MC Maheshwari from the department of Neurology, Neuroscience's center All India Institute of Medical sciences New New Delhi India.

Large numbers of families with many members having seizures have been used to understand the role of hereditary factors in the pathogenesis of human epileptic syndromes. The aim was to establish genetic database to form a hypothesis on the possible genetic contributions in different epileptic syndromes .The study concluded that A significant percentage (19%) of first and second degree relatives of probands with all types of epileptic syndromes have seizures

- *The risk of relatives being affected varied as a function of relation with the proband. Concordance of epileptic syndromes between probasnds and relatives was related to the epileptic syndromes in probands.*

- *The syndrome of SSEL is probably a benign epileptic syndrome seen in Indians genetically predisposed to seizures. Hereditary factors may play an almost*

equal role in the predisposition of relatives of epilepsy in families of probands with different epileptic syndromes.

In another study by S. Jain, Menka S. Jain, M V Padma, A Puri, P. Sen and M C Maheswari from department of Neurolrology, Neuroscience's Center AIIMS New-Delhi India on Epilepsies among twins born in families of Indian probands with epilepsy had following conclusions-

1.The-twinning rate among families of Indian probands with epilepsy is similar to that seen in data from hospital births in the same city and other studies reported from India

2. Epilepsy in twins may be largely genetic rather than due to factors associated with twinning

3.Family data such as in this study, if collected meticulously, can be used to form hypothesis for understanding the extent of contribution by genetic factors towards the pathogenesis of complex genetic diseases like human epilepsies.

In another study by S. Jain, Padma M V, Tripathi M, Narula A, Seema, Gujreet and MC Maheswari on Phenotypic analysis of JME:

Implication for gene discovery strategies the conclusion was that persons diagnosed with JME having absence (7%) overlap with absence epilepsy. JME affected having PPR on EEG (8%) and those needing VPA and another drug for seizure control (10%) could be the other subtypes. Among all JME there could be about 25% who may have not the classical syndrome. The familial and sporadic cases could be other subgroups. These possible sub types could be responsible for confounding result of genetic studies (Paper presented at the Asia and Oceanian Congress 11-13Nov. 2000 New Delhi India)

Aims and objectives of the study

1. To classify the seizure types in the children among the Family members of railway employees

2. To know the incidence of past history of febrile convulsions in the Children presenting with different seizure types

3. To know the occurrence of seizures among family members.

Material and methods

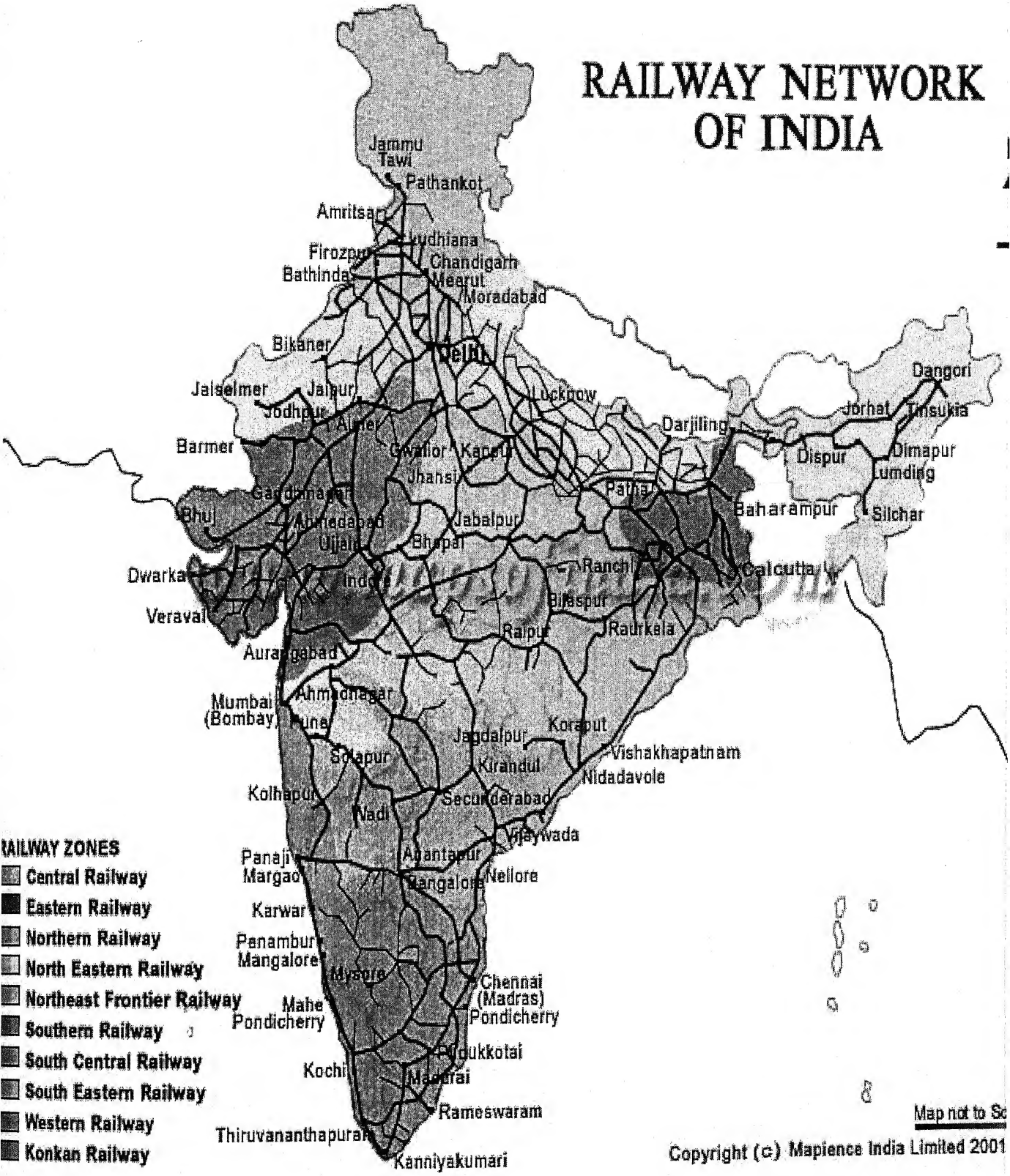
The present study was carried in the department of Pediatrics at Northern Railway Central Hospital, New Delhi. The entire study group consisted of Railway Health Services beneficiaries. Two hundred and eighty six children who attended NRCH, out patient department or indoor department or admitted through the causality in the age group up to 16 years were included in the study.

The Northern Railway Central hospital is referral hospital for whole of Northern Railway and surrounding area of other Zonal Railways. The map on the next page shows the geographical area from where these patients have been coming to central hospital.

The geographical areas of Punjab, Haryana, Utter Pradesh and some parts of Rajasthan and Delhi as a whole are included in Northern Zone.

The map showing geographical area of residence of patients is shown on the next page:

RAILWAY NETWORK OF INDIA



RAILWAY ZONES

- Central Railway
- Eastern Railway
- Northern Railway
- North Eastern Railway
- Northeast Frontier Railway
- Southern Railway
- South Central Railway
- South Eastern Railway
- Western Railway
- Konkan Railway

Map not to Sc

The Railway workforce is permanent employees of the organization are stable population as continuation of the job up to sixty years of age make a more suitable group for prolonged follow up of the probands and their families. The follow up is easier than city mobile population. The railways give comprehensive treatment to all Railway employees. The transportation up to and for for attending NRCH is free. All investigations including neuroimmaging studies and serum level studies for AED levels and pharmaceuticals are free irrespective of the cost.

Railway population is subset of population in India where the socioeconomic status, permanent employment total free and readily accessible quality comprehensive health care is available to all the beneficiaries, There is no waiting for specialist advise at NRCH. All patients requiring indoor admission or OPD consultation are given the same on same day. Or the availability of health facilities is available to them at par of any developed country in the world

All patients were attended between september1998 to 1999 were included in the study. Complete clinical details were recorded. History of febrile seizure was included in clinical details of the patients. The details were recorded on a Performa.

Performa has been annexed.

Details of EEG were recorded. EEG facility is available in NRCH. All EEG's were personally reported by trained Neuro-Psychiatrist of the hospital.

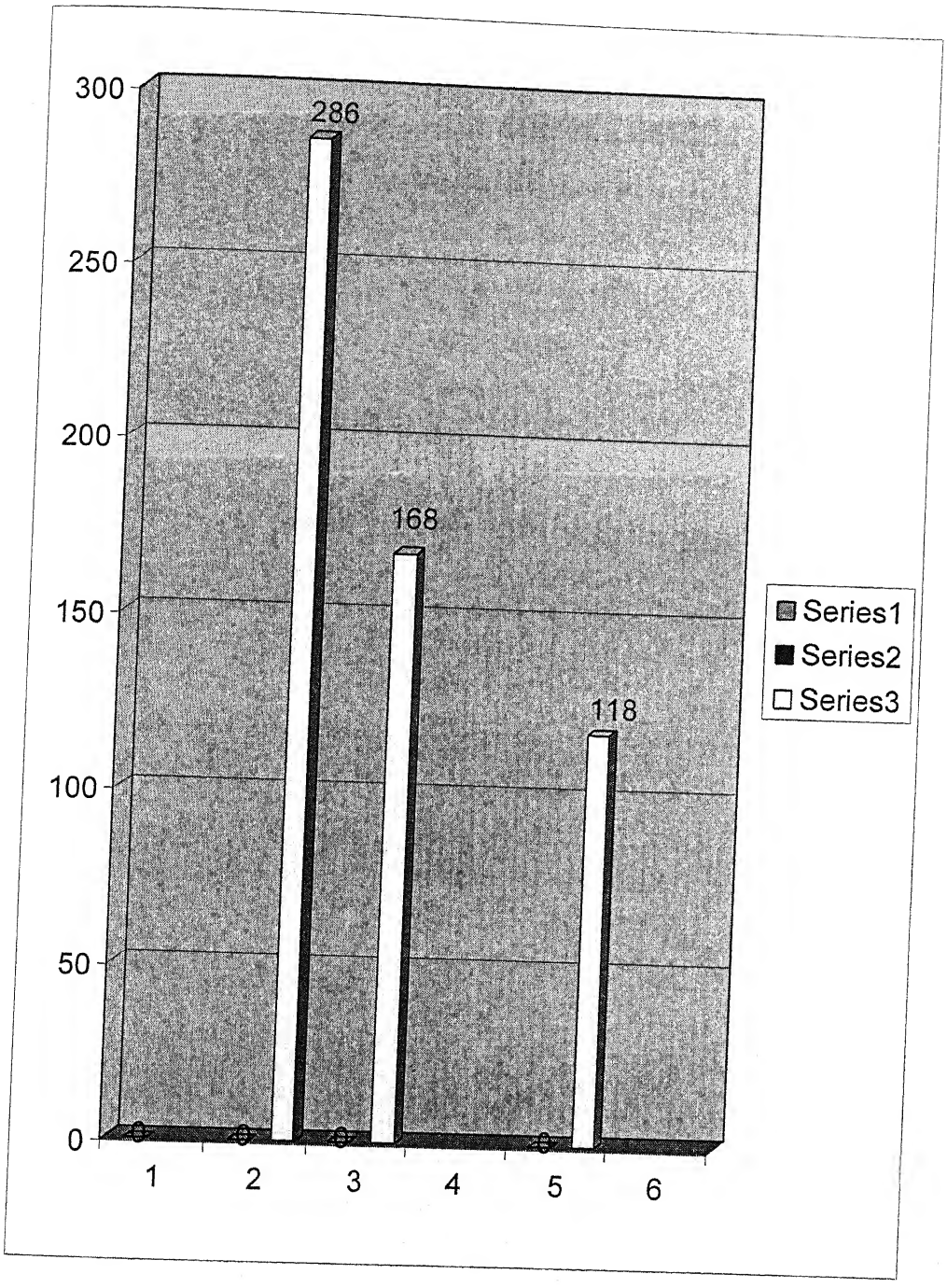
The classification of epilepsies and epileptic syndromes were done on the basis of revised classification given by International commission on classification and terminology of the International League Against Epilepsy 1989.Th classification of ILAE-89 is annexed.

The family pedigree was constructed to include all first degree and second-degree relatives of the probands. Seizures in the family members were documented and effort was made to examine all the available affected relatives.

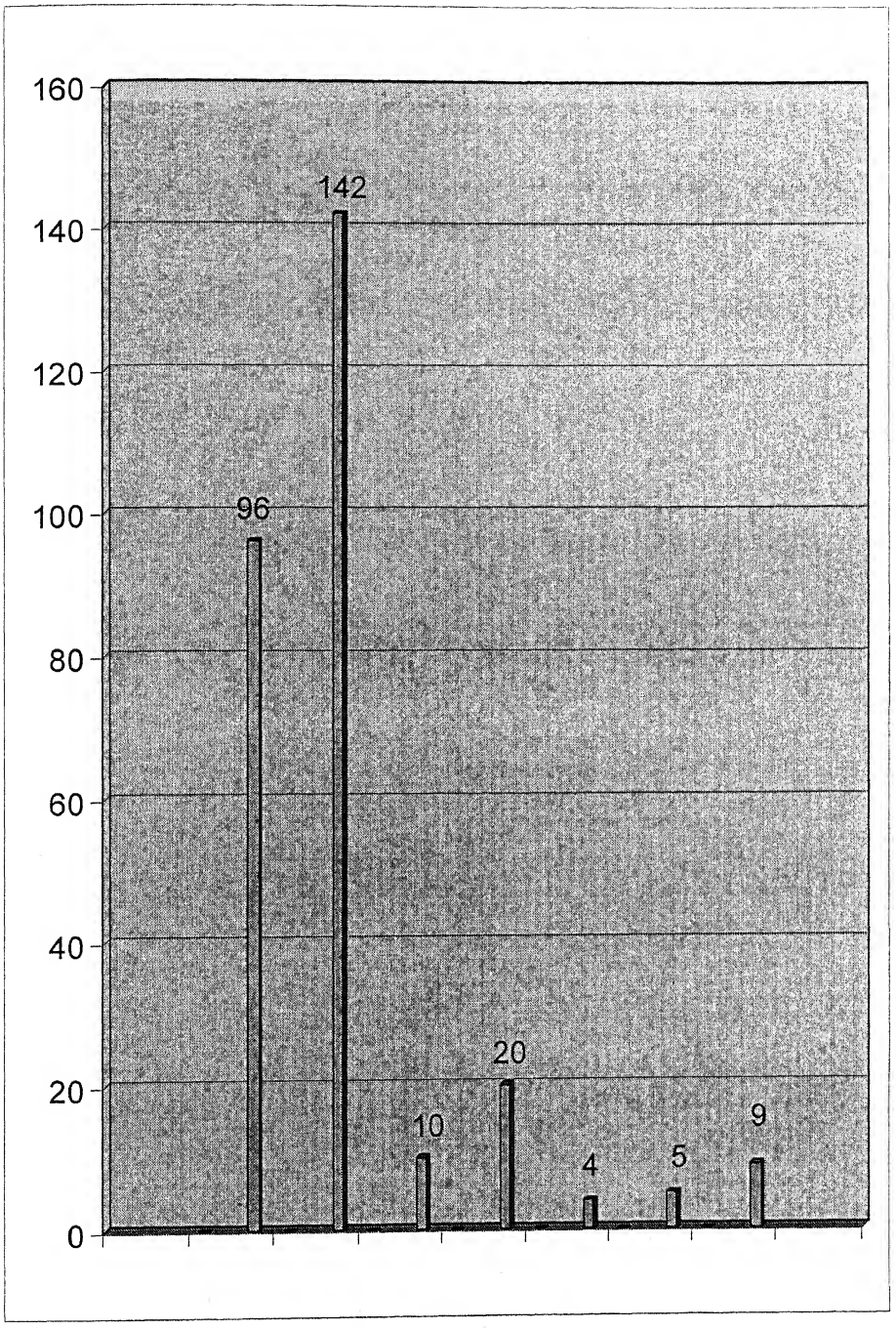
The seizure classification and entire family data was verified on every visit of the patient.

- ***Data and observations***

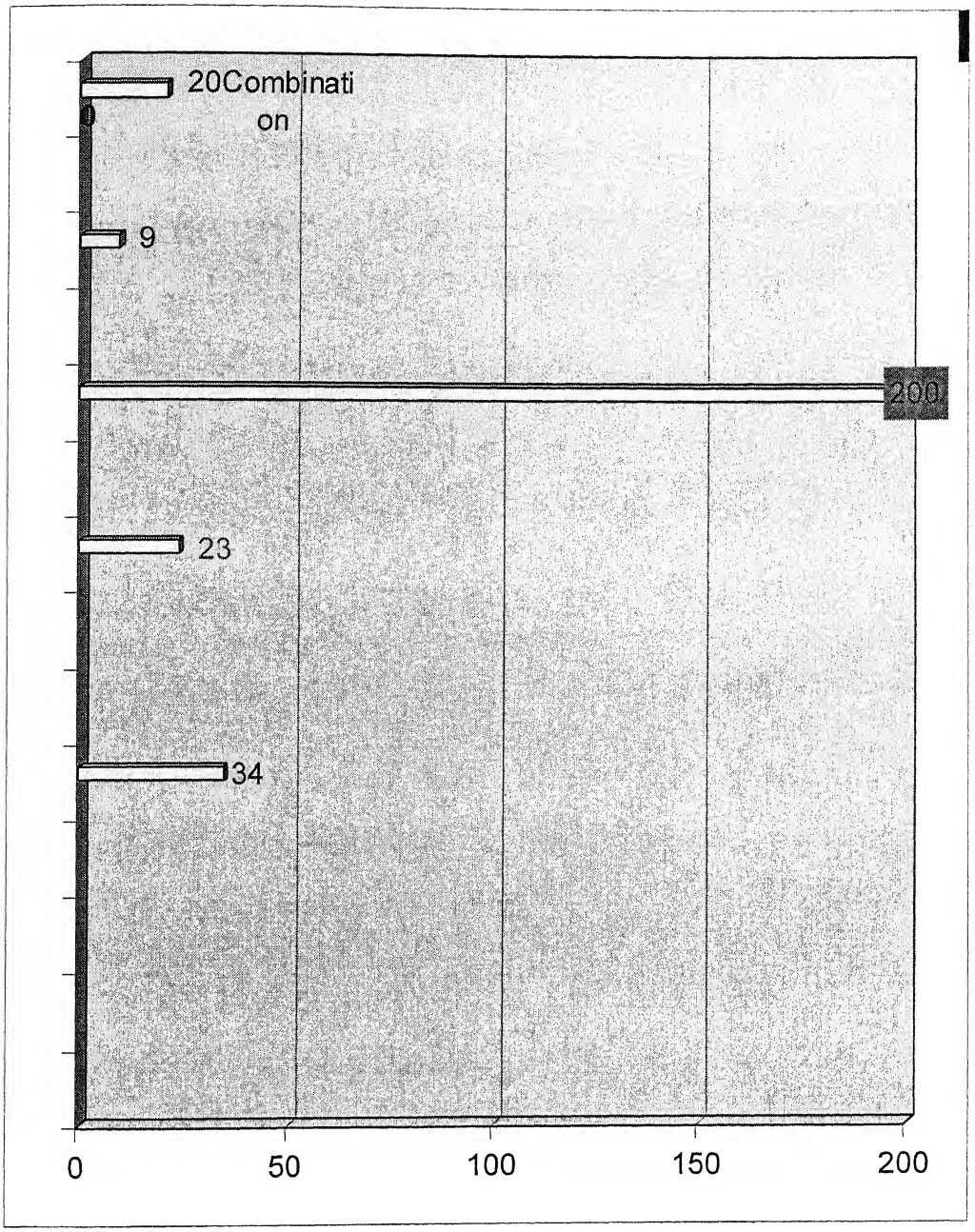
Male- Female ratio	
Total two hundred and eighty six cases have been included in the study. ***One hundred and sixty eight probands belonged to male sex.***	
Total cases	***286***
Female patients	***118***
Male patients	***168***


300
250
200
150
100
50
0
286
168
118
1
2
3
4
5
6
Series1
Series2
Series3

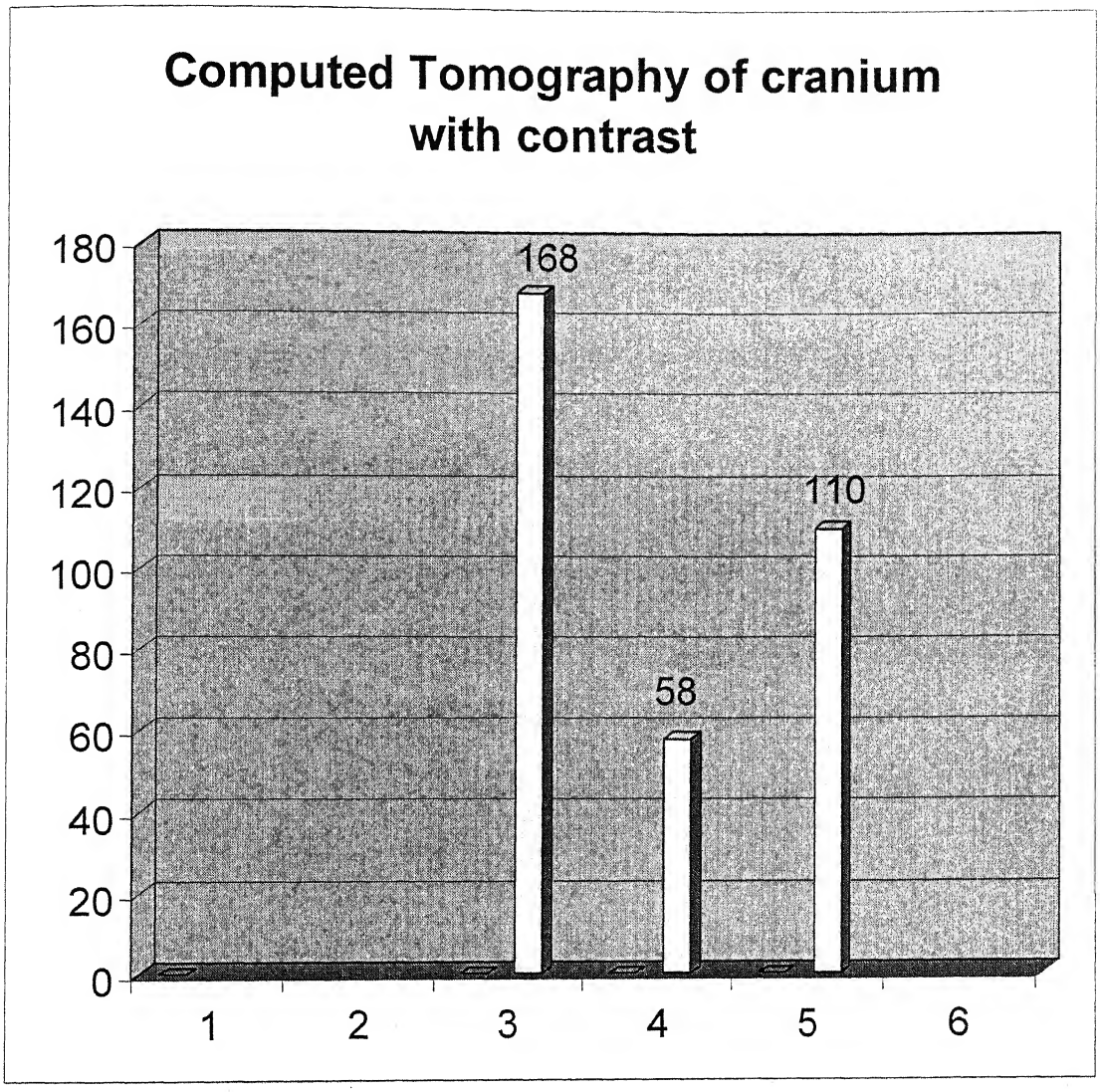
Classification: Seizure Type		
History based :		
1.	Focal/partial /sec generalized Sz.	096
2.	Generalized tonic or clonic or tonic clonic Sz.	142
3.	Juvenile Myoclonic epilepsy	010
4,	Childhood absence epilepsy	020
5.	West syndrome	004
6.	Single Sz	005
7.	Febrile seizures	009


160
140
120
100
80
60
40
20
0
142
96
10
20
4
5
9

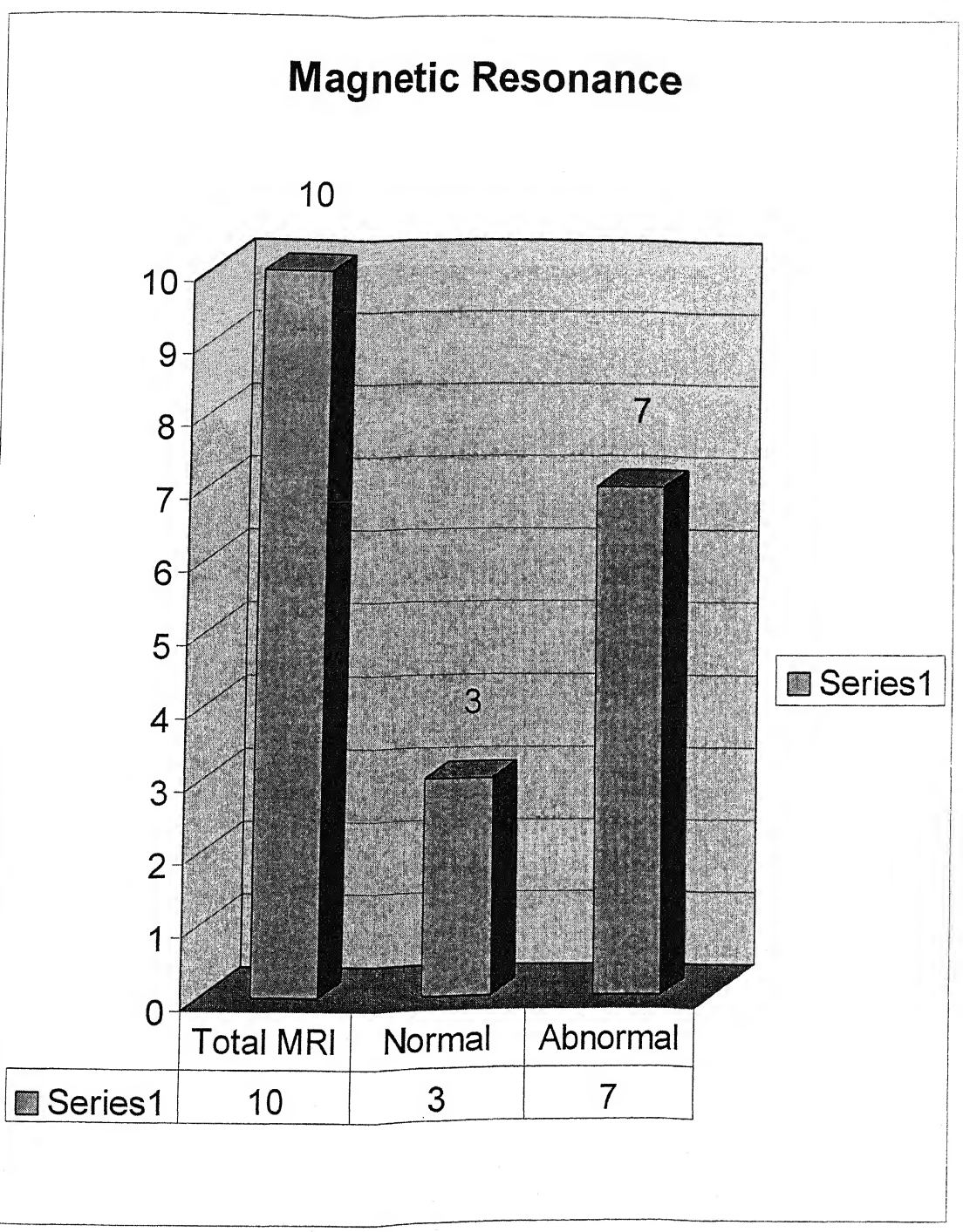
Anti Epileptics used	
Sodium Valproate	034
Clobazam	009
DPH	023
Carbamezepine	200
Combination	020


20Combinati
on
9
200
23
34
0
50
100
150
200

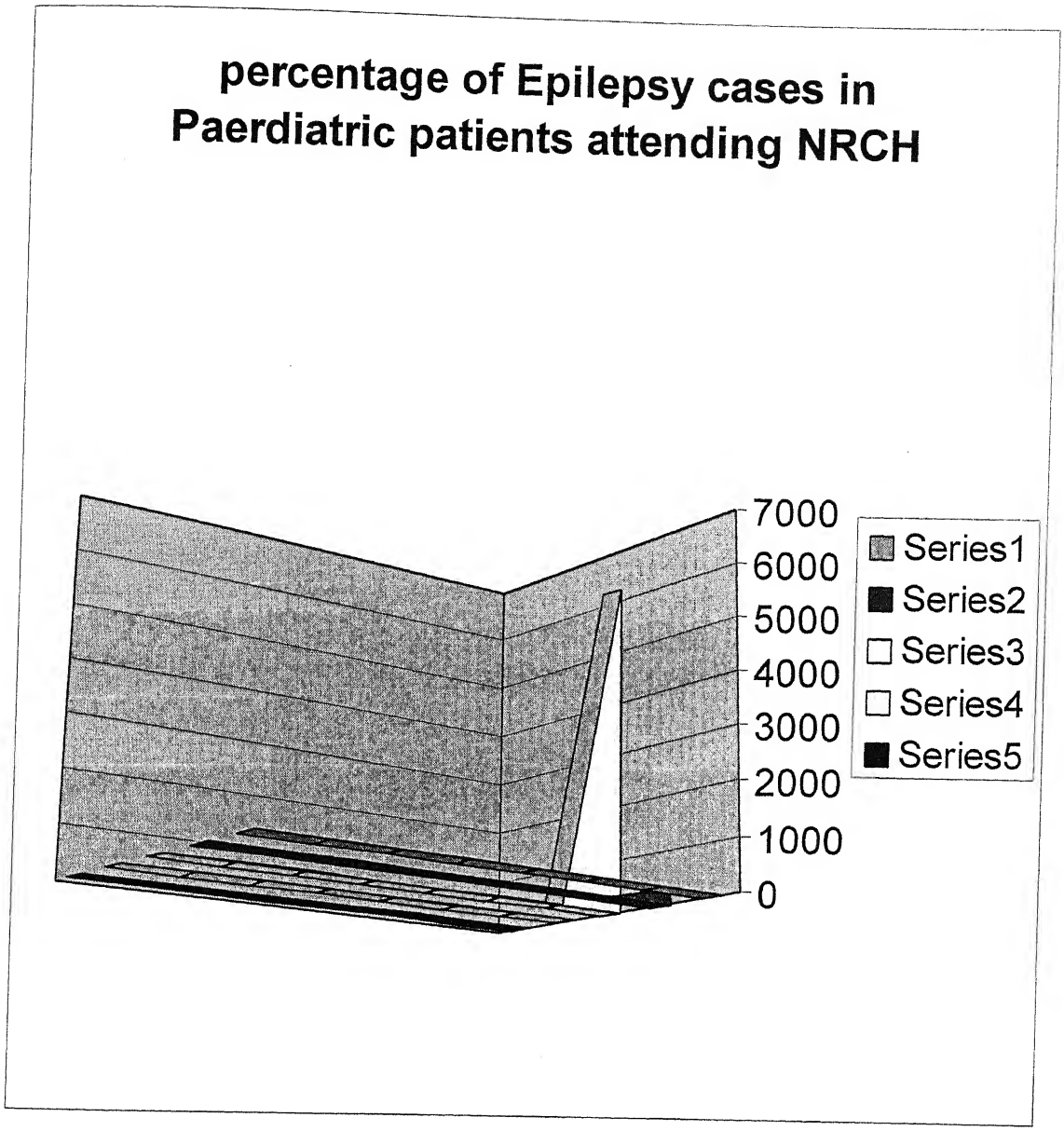
Computed Tomography done	
Total CT done	168
Normal	58
Abnormal	110


Computed Tomography of cranium with contrast
180
160
140
120
100
80
60
40
20
0
168
58
110
1
2
3
4
5
6

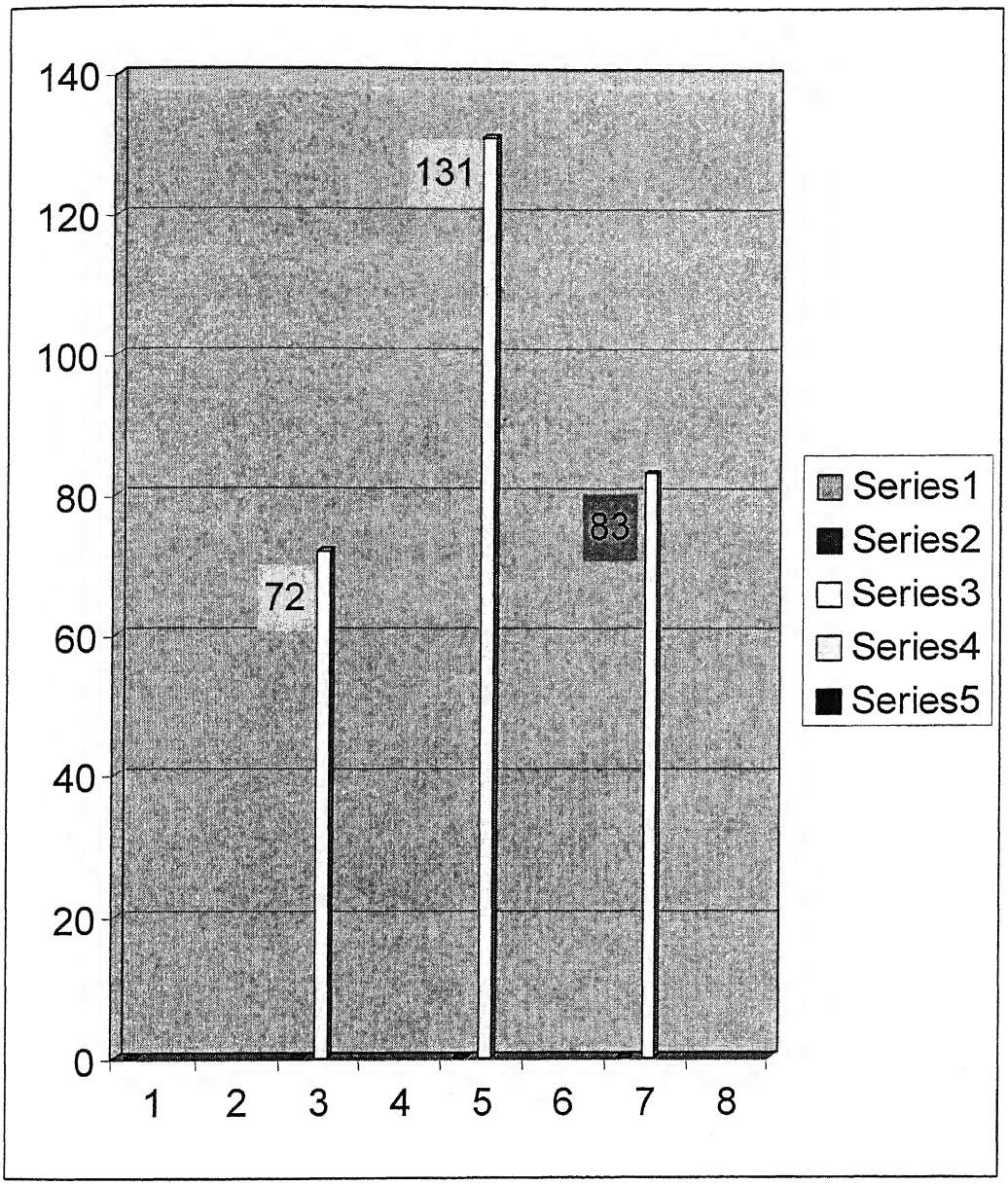
Magnetic Resonance (MRI)	
Total MRI	***10***
Normal	***03***
Abnormal	***07***


Magnetic Resonance
10
10
9
8
7
6
5
4
3
2
1
0
7
3
Series1
Total MRI
Normal
Abnormal
Series1
10
3
7

Percentage of epilepsy cases in total pediatric Patients attended at NRCH	
Total pediatric patients attended NRCH during this period-	6234
Total number of seizure cases in children	286
Percentage of epilepsy cases among total pediatric Patients attending NRCH	4.57%

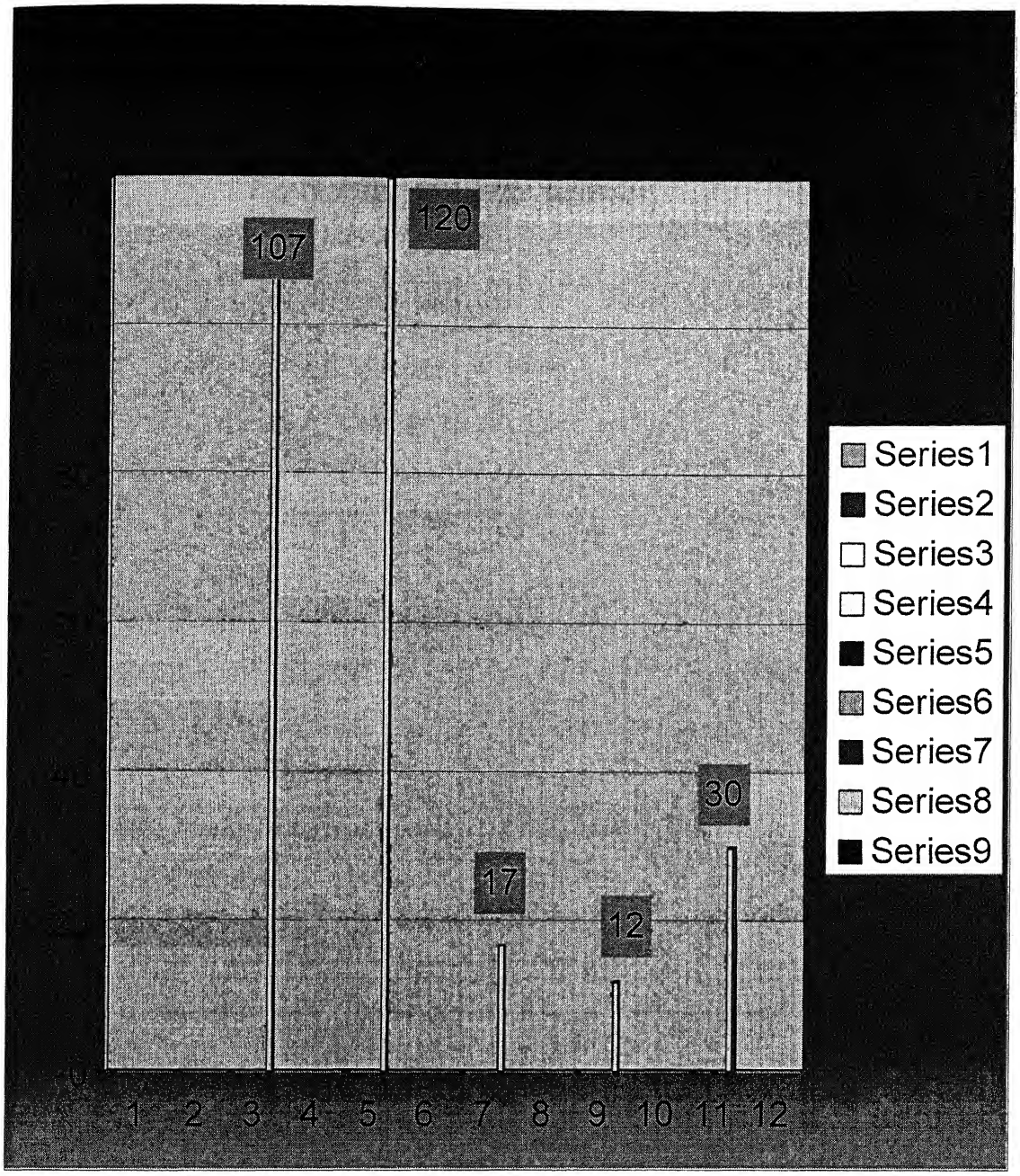

percentage of Epilepsy cases in Paerdiatric patients attending NRCH
7000
6000
5000
4000
3000
2000
1000
0
Series1
Series2
Series3
Series4
Series5

Age wise distribution of seizure disorder in children	
0-5 years	*72*
6-10 years	*131*
11-16 years	*83*
Total children attended at NRCH for seizure disorder	*286*



Age wise distribution of seizure disorder in children	
0-5 years	72
6-10 years	131
11-16 years	83

Syndromic classification of seizures after EEG, Nueroimmaging studies and other required investigation (Classification as per ILAE-89)	
1. Localization related- epilepsies and syndromes	***107***
2. Generalized epilepsies and syndromes	***120***
3. Epilepsies and syndromes undetermined,	***017***
Weather localized or generalized Focal/ Generalized, Neonatal Sz	
4. Special syndromes. Febrile Sz, Single Sz, Situation related Sz.	***0 12***
5. Seizure with single Small Enhancing CT Lesion (SSEL)	***030***



Syndromic classification of seizures after EEG,Neuroimmaging and other investigations in protocol
Classification as per ILAE-89

1.Localisation related epilepsies and syndromes	107
2.Generalised epilepsies and syndromes	120
3.Epilepsies and syndromes undetermined	17
4. Special syndromes-Single Sz,Febrile Sz,Situational Seizures	12
5.Seizures with single Small ring Enhancing CT lesion	30

Percentage of febrile seizures	
Total no of cases of epilepsy	*286*
History of febrile seizures present in	*15*
%age of febrile seizures in the study group	*5.24*

Cases where family history was positive in the family of Probands	
Total cases of Epilepsy	*286*
Family history positive in	*60*

Discussion

*It has been estimated that 50 percent of epileptic cases has its onset in pediatric age group. In our study out of total six thousand and thirty children who attended the pediatric dept of NRCH from Sept.1998 to Aug 1999. Incidence of epilepsy for all age group is about 40/100,000 person years (Hauser WA,Annegers JF, Kurland LT. The incidence of epilepsy in Rochester, Minnesota 1935-79, Epilepsia 1984; **25**:666). There were two hundred and eighty six cases of epilepsy, which are approximately 4.67 % of total attendance NRCH in Pediatric department. It is less in comparison to developed countries because our beneficiaries are habituated in a linear fashion along the Railway track and big proportion do not come to NRCH for obstratic care during child birth. This the main reason that in our study the maximum cases of epilepsy are in age group of 6 to 10 years age bracket. In all other studies the percentage of first Sz is maximum in 0 to 1 year (Peter R. Camfield and Carol S. Camfield Pediatric epilepsy: an over view chapter 37: pp637).*

In our study the number of male affected children is higher which is compatible to the existing literature.

Seizure types have been classified on the basis of history and clinical examination first and followed by using Syndromic classification given by International League Against Epilepsy in 1989(Epilepsia 1989) after work up of cases like compulsory EEG, Haemogram, CXR, CT/MRI if required and fundus examination (in every case), Mauntox test and Serum IgG etc for Neurocysticercosis if required. Serum lavels were done for levels of anti epileptic medicines where seizure control was poor. Sodium Valproate has been used where Idiopathic generalized epilepsy was diagnosed as absence or Myoclonic type and where carbamezepine was not leading to good seizure control. The Carbamezepine has been main stay of treatment in most general tonic clonic type of seizure disorder and partial seizures. Cost of medicine and availability was not the issue as Railways free of cost supply all pharmaceuticals. The follow up was quit regular because the transport and medicine and all investigations to railway beneficiaries are free. The availability of specialist for consultation is easily accessible on all working days of the hospital. The admission to children is not denied even if the wards are over crowded. The specialist service to the patients is available to patients on all days and odd hours also through emergency department of the hospital.

The syndromic classification has been useful for managing the epileptic cases for following reasons

- *Judicious uses of anti epileptic drugs like Sodium Valproate in absence and Myoclonic Epilepsy.*
- *When to start AED.*
- *When to withhold the medicine.*
- *When to withdraw medication: for example in Benign Centro-temporal epilepsy one can withdraw the medicine early or even with hold the AED but one has to continue medicine for prolonged period in Occipital epilepsy.*
- *To predict the prognosis for example in Juvenile myoclonic epilepsy AED has to be for prolonged or life long need. The prognosis of West Syndrome is bad in comparison of Benign Rolandic epilepsy.*

The Syndromic classification gives more accuracy in diagnosis like EEG in Absence epilepsy where 3 Hz per sec spike is almost the signature of the disease with this one can be accurately administer AED (Sodium Valproate) and give prognosis of the disease. If EEG slow spike wave paroxysms of less than 2.5 Hz on an abnormal background activity, commonly is associated with mental retardation as is seen in Lannox Gastot Syndrome.
ILAE classification of 1989 which appeared in epilepsia1989; 30:389-399 is syndromic classification. The syndromes are clusters of signs and symptoms customarily occurring together and include-

- *Clinical event*
- *Age of onset*
- *Ictal and interictal EEG*
- *Evolution and prognosis*
- *Associated neurological features*
- *Family history*
- *Neuroimmaging*

In our studies idiopathic generalized epilepsies are more as in other studies of India and abroad one is of Oka ET AL (J Epilepsy 1993; 33:1072-7) .The symptomatic epilepsies are more in India because of incidence of perinatal insult and CNS infections and SSEL. Probands had a family history comparable to that those of GES. The syndrome of SSEL

appears to be benign epileptic syndrome seen in the Indian population that is genetically predisposed to seizures. (S.Jain ET alEpilepsia.Vol.38.no, 1997)

The use of ILAE classification 89 was used in our study in two hundred and eighty six cases presented to us in NRCH. The classification was useful in management and predicting the prognosis of the cases. It is recommended that every children pediatric neurology division should adopt in protocol to classify the seizures, This will improve the quality of management of epilepsy in children. There is some need to make classifiation more users friendly as this classification is complex and many syndromes are not adequately defined. The other limitations of seizure classification is that it describes common seizure phenomenology only and can not reliably distinguish partial from generalized origin of seizures is a crude guide to selection of drug treatments as per Dr Engels "A major contribution of the International League against Epilepsy was the establishment of standardized classification and terminology for epileptic seizures and syndromes. This provides a universal vocabulary that not only facilitated communication among clinicians, but also established a taxonomic foundation for the performance of quantitative clinical and basic research on epilepsy. The Executive committee of the ILAE, which took office in July in 1997, is reviewing the current classification we now await a new user-friendly classification, which may include pathophysilogical Substrates, underlying gene defects and functional disability due to epilepsy.

Febrile seizures:

In our study nine cases were purely of febrile seizures, that is approximately three percent of the study group. The children with the epileptic syndromes who had history of febrile convulsions were only 1% in our study group. These children were separate then purely febrile seizure children who were in age group of 3 years to 5 years of age proves that febrile seizure is not a major risk factor for subsequent epilepsies in children. In our study only ten MRI were done so no comment can be given regarding association between Mesial Sclerosis and febrile convulsions. However studies shows that (Camfield PR, Camfield CS.Management of febrile seizures. Current problems in Pediatrics 1997; 27(1): 6-13) Mesial temporal sclerosis is only 1/75000 children. In our study group febrile patients were managed by intermittent prophylaxis with oral diazepam .It seems that counseling to alley the anxiety of parents should be main for this benign disorder.

Family history of seizure disorder in the family of probands:

In our study group of epileptic children sixty cases were having positive family history in first degree or second-degree relatives of the probands. This is 60% of the study group, which is comparable to other studied in this geographical area. Family history was more positive in the children who were having idiopathic generalized seizure disorder. The family history was also more common in the children who had EEG finding of Centrotemporal spikes (Benign Centro-temporal epilepsy)

The children who had febrile convulsions also had family history positive proving febrile seizure disorder a genetic inherited benign disorder. In one study at AIIMS by Satish Jain et al the family history in the first degree and second degree relatives was found to be 19% (S. Jain et al Occurrence of Epilepsies in family members of Indian probands with different epileptic syndromes; Epilepsia: 38(2): 237-244.1997).

In our study the family history is positive in sixty cases, which is approximately 20.97% of the study group.

Conclusion

In this study we have included two hundred and eighty cases of epilepsy that were presented to us in the department of Pediatrics at NRCH New Delhi from September 1999 to August 2000. The children were presented to us through casualty, Pediatric OPD or were admitted to the indoor department after referral from peripheral referral centers of Indian Railways. The geographical area from where children came has been Delhi and surrounding areas of Delhi, Railway population residing in Punjab, Uttar Pradesh, Haryana, Rajasthan and Utteranchal states of India. The study used ILAE-1989 classification and found that it is useful for management of the patients for following reasons

- *It allows the judicious use of ant-epileptic drugs (AED)*
  - *-When to start AED*
  - *-When to withdraw AED*
  - *-And help to decide when to withhold the medicine*
- *In predicting the prognosis of epilepsy in a particular child by knowing his classified group as per ILAE-89.*
- *For defining the likelihood of identifying the underlying pathology.*

In this study fifteen cases of febrile seizures were found in the total study group. The percentage of febrile seizures is same as found in general population in other studies. We conclude that febrile seizure is not a very significant factor in leading to epilepsy in children in later life. The family history in the cases of febrile seizures was present in significant numbers indicating it to be a genetic inherent disorder.

The family history was meticulously recorded in all the cases. The pedigree was made up to second degree relatives of the Probands. It has been found that family history was positive in sixty children who presented with epilepsy to this referral center. This figure comes to 20.97% of cases, which is consistent with other studies in this part of the world. The study is indicative that in epileptic syndromes in children hereditary plays a very important role. In the present study the symptomatic cases of epilepsy are in significant numbers. It is because the perinatal insults and CNS infections like tuberculosis and protozoa infestations like Taenia Solium are quite prevalent in this part of the world.

In age wise distribution in total study group of two hundred and eighty six epileptic cases 72 were in 0-5 years, 131 were in 6-11 years and 83 were in 11-16 years of age group.

The number of children in 0-5 years is less in comparison to available data in other national and international studies. This is because our population is residing in a linear fashion in the cities, towns and stations along the Railway track of Indian railways. The seizures in children are maximum in first twenty eight days of life the neonates are managed locally as few mothers comes for deliveries at NRCH form distant cities and towns and prefer confinement near their normal place of residence. In higher age group children are brought by the parents when seizures are recurrent needs neuroimmaging studies and other lab investigation like serum levels etc. This is a selection bias in our study because of different geographical distribution of our beneficiaries.

Recommendations

- *The present study was done in a subset of population in India. The study group was small the further study in a larger set up is required.*
- *The study proves that Classification of seizures using ILAE-89 should be adopted by all pediatric Neurology clinics as it helps in appropriate choice of AED.*
- *Family pedigree up to second degree relative should be drawn in all seizure cases.*
- *Neuroimmaging studies like CT/MRI should be part of protocol for all patients of epilepsy.*
- *The investigations to rule out CNS infections like Tuberculosis and protozoal infestations like Taenia Solium should be done.*
- *The febrile seizure is not a significant risk factor for epilepsy in later years of life.*
- *Family pedigree is helpful in pointing the underlying pathology of the diseases. The positive history also gives clue for choosing the AED.*

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- Appendix

Appendix-1

Performa used for the study of Epilepsy in children attending Railway central hospital New Delhi for degree of Doctor of Philosophy in Paediatric Medicine

Name.....Age/Sex.....reg.no.....

DATE OF BIRTH.....
Address.....
.....Pin code.....
Tele.no.....Res.....Office.....

Occupation...Education level.....

Past history of febrile Seizures.....

If yes, age of onset...Total FC.....

Present Seizure type.....

Seizure frequency..... <1year 1-6 /year >6/year

History of Todds Palsy.....

Treatment (name and dose per day.....

Seizure control No Seizures 1-4 Sz >then 4 Seizures

EEGdetails.....

If abnormal: ..... Generalised/focal/Focal with Generalised

CT/MRI ..... Normal/Abnormal

If Abnormal conclusion.....

Family history.....present/absent

Family pedigree.....
.....
If present Diagnostic Code.....

Final diagnosis and code...

Any other information----------

Appendix-2

Seizure Classification to be used for study of Epilepsy in children in a subset of population for degree of Doctor of Philosophy in Paediatric Medicine from Bundelkhand university, Jhansi.

SEIZURE CLASSIFICATION

1.1 Idiopathic- LRES

1.2 Symptomatic- LRES, CT/MRI: Abnormal

1.3 Cryptogenic- LRES, CT/MRI: Normal

Generalized Epileptic Syndromes (GES)

2.1 Idiopathic age related syndromes

2.2 Cryptogenic/Symptomatic

-West Syndrome/LG Syndrome
-With GTCS, MJ/ Abs. etc.

2.3 symptomatic Epilepsies/ syndromes with GTCS as presenting feature

3.0 Unclassified: Focal/ Generalized, Neonatal Sz, Others etc.

Special Syndromes

4.1 Febrile Convulsions (FC)

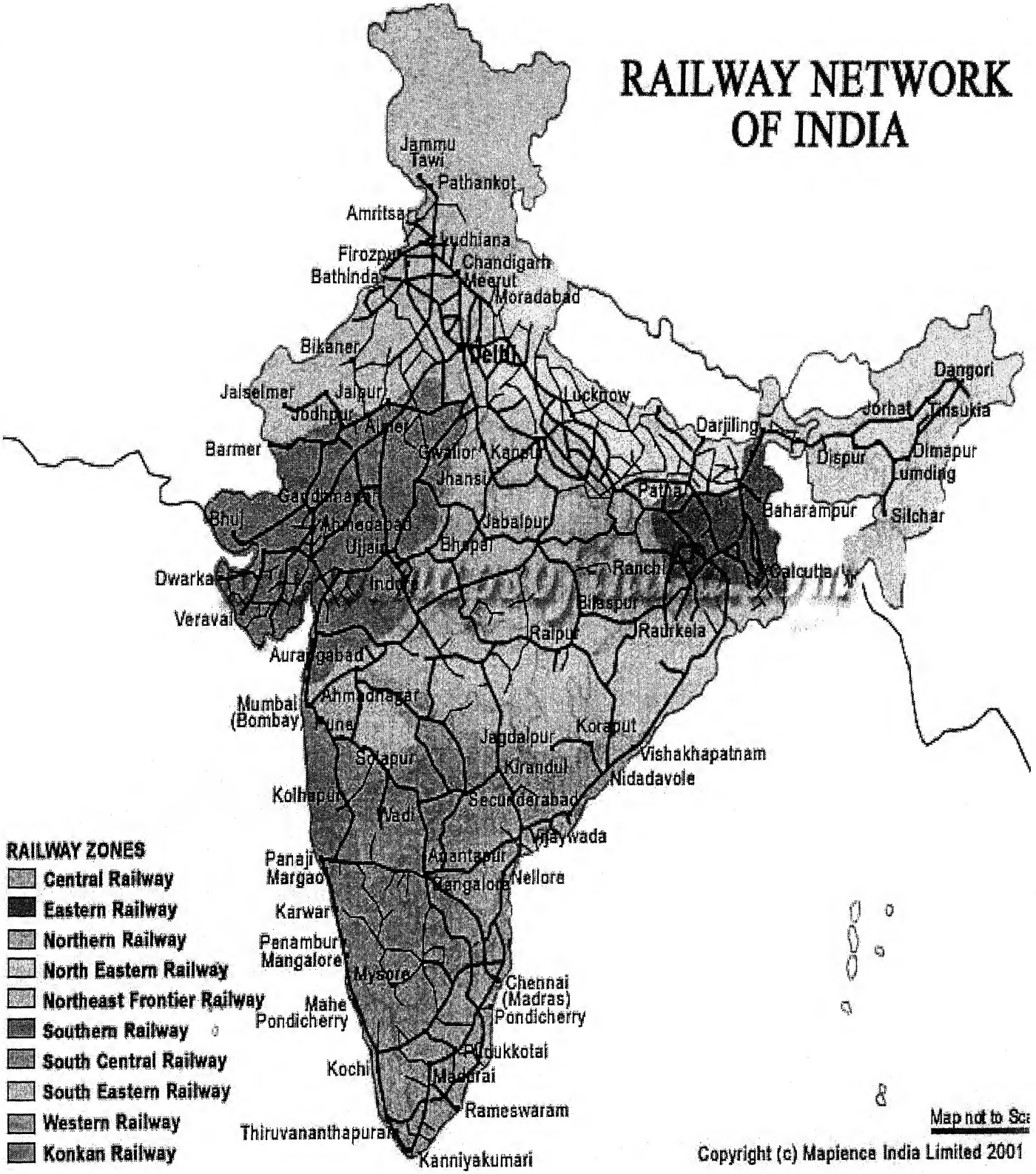
4.2 Single Sz (SSZ)

4.3 Situation related (SR) Sz associated with Alcohol / drugs / Ecampsia / Diabetes Ketoacidosis / Acute Metabolic events

5.0 Seizure with Single Small Enhancing CT Lesion (SSEL)

6.0 Others H/O Sz + but patients not seen dead relatives with H/o Sz.

RAILWAY NETWORK OF INDIA



Map not to Sc